REMARKS

Claims 1-13 are pending in the present application. Non-elected claims 14-39 have been cancelled without prejudice or disclaimer of the subject matter thereof. By this Amendment, claim 9 is amended. No new matter is added.

Claim Objection

Claim 9 is objected to for a minor informality. By this Amendment, claim 9 is amended as suggested by the Examiner. Reconsideration and withdrawal of this objection are respectfully requested.

Section 102(b) Rejection over ES '069

Claims 9-11 and 13 are rejected under 35 U.S.C. § 102(b) as being anticipated by ES '069 (Spanish Patent Application No. ES 2050069 to Marquillas Olondriz et al). Applicants respectfully traverse this rejection.

Claim 9 is directed to an enriched Z-isomer oxime of formula (3) or (7), in which the amount of the Z-isomer is at least 80% based on the total amount of the oxime. As described in the present specification, ES '069 discloses an oxime of the formula (7) (see pp. 2-4 of the specification). ES '069 is silent regarding any specific amount of Z-isomer in the disclosed oxime. Accordingly, ES '069 does not expressly teach the claimed amount of Z-isomer.

The Examiner asserts that ES '069 inherently teaches the claimed amount of Z-isomer, based on ES '069's disclosure of an 84.7%[1] yield of a cyclized product made

[1] The Examiner indicates that ES '069's Example 10 describes a yield of the cyclized product of 87.7%. Example 10 actually describes a yield of 84.7%. See col. 8, line 1, of ES '069.

using the oxime. In particular, the Examiner assumes that because the E-isomer is unreactive, the Z-isomer must have been present in excess of 90% in order to achieve the 84.7% yield. The Examiner's assumption that the Z-isomer *must* have been present in excess of 90%, however, is unreasonable.

As noted by the Examiner, the E-isomer of the oxime can be converted into the Z-isomer. See specification at page 10, lines 14-15. In fact, ES '069's cyclization reaction occurs in the presence of sodium hydride, which is a reactive agent that causes a base-mediated kinetic isomerisation of the Z-isomer to the E-isomer (see ES '069 at col. 7, lines 33-34). Accordingly, it is not necessary for ES '069's Z-isomer to have been present in excess of 90% in order to achieve the 84.7% yield, because as the Z-isomer is being cyclized, the supply of Z-isomer may be replenished by the conversion of the E-isomer to the Z-isomer. Thus, the 84% yield does not necessarily require an initial high isomeric purity, as the Examiner contends, but could simply be the result of equilibrium forces surrounding the conversion to (isomerisation) and reaction (cyclization) of the z-isomer.

The fact that a certain result or characteristic may occur or may be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578 (CCPA 1981). Inherency may not be established by probabilities or possibilities. *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999). Because it is not necessary for ES '069's oxime to include the claimed amount of Z-isomer (because the E-isomer can be converted to the Z-isomer), ES '069 does not inherently teach the claimed amount of Z-isomer.

Accordingly, ES '069 does not expressly or inherently teach the claimed amount of the Z-isomer of at least 80%, and ES '069 thus does not anticipate claims 9-11 and 13. Reconsideration and withdrawal of this rejection are respectfully requested.

Section 102(b) Rejection over Kennis

Claims 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Kennis (U.S. Patent No, 4,804,663). Applicants respectfully traverse this rejection.

Claim 9 is discussed above with reference to ES '069. As described in the present specification, Kennis discloses an oxime of the formula (3) (see pp. 1-2 of the specification). Kennis is silent regarding any specific amount of Z-isomer in the disclosed oxime. Accordingly, Kennis does not expressly teach the claimed amount of Z-isomer. Furthermore, as discussed below, Kennis' Example 1 can produce only the oxime hydrochloride salt, which is excluded from claim 9 as presently-recited.

1. Kennis does not teach the claimed amount of Z-isomer

The Examiner asserts that Kennis' oxime of Example 1 inherently includes the claimed amount of Z-isomer, because Kennis discloses a 61.8% yield of a cyclized product made using the oxime (i.e., 6.8 parts of the cyclised product made using 11 parts of the oxime) (see col. 11, lines 10-17 of Kennis). The Examiner assumes that because the E-isomer is unreactive, the Z-isomer must have been present in excess of 90% in order to achieve the 61.8% yield. The Examiner's assumption that the Z-isomer *must* have been present in excess of 90% is, however, unreasonable.

First, the Examiner has provided no basis in fact and/or technical reasoning why it is necessary for Kennis' oxime to include the Z-isomer in excess of 90% to achieve a

product yield of 61.8% (over a 25% difference). In fact, it is unreasonable to assert that such a high percentage of the Z-isomer is necessary to obtain a mere 61.8% product yield. Second, as discussed above with reference to ES '069, the E-isomer of the oxime can be converted into the Z-isomer *in situ*. Accordingly, it is not necessary for Kennis' Z-isomer to have been present in excess of 90% in order to achieve the 61.8% yield, because as the Z-isomer is being cyclized, the supply of Z-isomer can be replenished by the conversion of the E-isomer to the Z-isomer.

The fact that a certain result or characteristic may occur or may be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578 (CCPA 1981). Inherency may not be established by probabilities or possibilities. *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999). Because it is not necessary for Kennis' oxime of Example 1 to include the claimed amount of Z-isomer (because the E-isomer can be converted to the Z-isomer), Kennis does not inherently teach the claimed amount of Z-isomer.

Accordingly, Kennis does not expressly or inherently teach the claimed amount of the Z-isomer of at least 80%, and Kennis thus does not anticipate claims 9-12.

2. Kennis does not teach the claimed enriched Z-isomer free base

An attempt was made to repeat Kennis' Example 1 to determine whether Kennis' oxime could possibly include an amount of Z-isomer of at least 80%. Specifically, a reaction mixture was provided as disclosed in Example 1 (where "parts" was understood to mean "weight parts") (see Kennis at col. 11, lines 1-5). After the 3 hours reflux (see Kennis at col. 11, lines 5-6), a suspension was obtained. A sample of the suspension was taken directly from the reaction mixture, dissolved entirely in the HPLC mobile phase,

and analyzed by HPLC. Then, the reaction mixture was cooled and the solid product was filtered off, dried, and analyzed. The mother liquor after filtration was also analyzed. Then, the entire experiment was repeated. The results for the reaction mixture, the solid product, and the mother liquor for both experiments are shown in the following chart, in which the percentages are expressed as relative percentages of the HPLC peak intensities.

Chart

	(E)- oxime	(Z)- oxime	Starting ketone
Reaction Mixture:			
Experiment 1	40.33 %	53.12 %	0.93%
Experiment 2	33.28%	61.38%	2.70 %
Solid Product:			
Experiment 1	3.33 %	93.75%	2.49%
Experiment 2	1.16%	96.19%	2.65%
Mother Liquor:			
Experiment 1	46.25%	3.27%	18.16%
Experiment 2	74.79%	18.71%	5.31%

Experiment 1 Yield = 8.7 parts; Experiment 2 Yield = 8.16 parts.

As shown in the above Chart, the repeat experiments indicate that the solid product oxime in Kennis' Example 1 may include greater than 90% Z-isomer, although the yield from the repeat experiments was much lower than the yield of Kennis' Experiment 1. Because of this lower yield, one cannot reasonably conclude from the repeat experiments that Kennis' oxime necessarily includes greater than 90% Z-isomer. For example, the higher yield in Kennis may be due to a higher amount of the E-isomer in Kennis' oxime as compared to the solid product of the repeat experiments, caused by e.g. different "cooling" conditions or some other variable.

Moreover, the repeat experiments only form Kennis' oxime as a hydrochloride salt (i.e., not as a free base).

Specifically, the starting materials in Kennis' Example 1 were the ketone hydrochloride and the hydroxylamine hydrochloride at a ratio of 0.046:0.173 molar parts, resulting in 0.219 molar parts of hydrochloric acid present in the reaction mixture. The relative molar amount of the triethylamine added to the mixture was 0.104 molar parts. This amount of triethylamine could react with 0.104 molar parts of the hydrochloric acid, leaving a significant excess of hydrochloride acid. Indeed, an analysis of the chlorine content in the precipitated solid product of the repeat experiments confirmed that the resulting oxime was a hydrochloride salt, as the content of chloride ions in the solid product was 14.83% (which is slightly above 1 molar equivalent of hydrochloric acid with respect to the oxime). The reaction of the ketone hydrochloride with the large molar excess of hydroxylamine hydrochloride in Kennis' Example 1 thus provided for a mixture of the hydrochlorides of the Z- and E-isomers of the oxime. Because an excess of hydrochloride acid is present at all times during the reaction in Example 1, the Z-oxime of the solid product is likely only formed as a hydrochloride salt and not as the base as per claim 9.

Accordingly, Kennis does not teach the claimed enriched Z-isomer free base, and for this additional reason, Kennis does not anticipate claims 9-12. Reconsideration and withdrawal of this rejection are respectfully requested.

Section 103(a) Rejection over Strupczewski

Claims 1-8 are rejected under 35 U.S.C. § 103(a) as being obvious over Strupczewski (U.S. Patent No. 4,408,054). Applicants respectfully traverse this rejection.

Claim 1 is directed to an acetic acid salt of a compound of formula (3) or (7). The claimed acetic acid salt can be used to provide an enriched Z-isomer oxime of formula (3) or (7) to be used in an enhanced method of producing risperidone, which may include the cyclization of the enriched Z-isomer oxime. See the specification at page 6, lines 6-13, and page 12, lines 12-23. Strupczewski discloses an oxime in Example 25 that is used in an allylation reaction to form an allylated oxime hydrochloride (col. 25, line 63 to col. 26, line 15).

1. Lack of *Prima Facie* Obviousness

The Examiner asserts that it would have been obvious to a worker skilled in the art to modify the oxime of Example 25 to be an acetic acid addition salt thereof because (i) "This oxime intermediate is used for the exact same utility, the cyclization to the corresponding benzisoxazole," and (ii) "The only definition of salts ... lists 9 different pharmaceutically-acceptable salts. Acetic acid is one of the salts mentioned, and therefore, acetic acid would be an obvious choice to use for compound (3)." Each of the Examiner's assertions is in error.

First, the oxime in Example 25 of Strupczewski is not cyclized to form a corresponding benzisoxazole. In contrast to the Examiner's incorrect assertion, the oxime in Example 25 is used in an allylation reaction to form an allylated oxime hydrochloride (as mentioned above) (see also col. 8, lines 37-44). The Examiner has misinterpreted Example 25 of Strupczewski.

Second, a worker of ordinary skill in the art would not have been motivated to modify the oxime of Example 25 to be an acetic acid addition salt thereof merely because acetic acid is mentioned in Strupczewski. In fact, Strupczewski describes the various

pharmaceutically-acceptable salts only in the context of the benzisoxasole cyclized products that are to be administered to subjects. The oxime of Example 25, however, is not itself a cyclized product. Furthermore, neither claim 1 nor Example 25 of Strupczewski limit the salts of the oxime to being pharmaceutically-acceptable salts, nor is the oxime described as being administered to subjects. Accordingly, there would have been no motivation for a skilled worker in the art to select one of the nine pharmaceutically-acceptable salts of the benzisoxasole cyclized products for the oxime of Example 25. Other than merely locating the words "acetic acid" and "salt" in Strupczewski, the Examiner has failed to provide any suggestion or motivation in the prior art for a skilled worker to modify the oxime of Example 25 to be an acetic acid addition salt thereof.

Because the Examiner has failed to provide motivation for one of ordinary skill in the art to modify Strupczewski's oxime of Example 25 to be an acetic acid addition salt thereof, the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, claims 1-8 would not have been obvious over Strupczewski. Reconsideration and withdrawal of this rejection is respectfully requested.

2. Dependent Claims 4-8

The Examiner has failed to address any of the limitations of dependent claims 4-8. Strupczewski, however, does not teach or suggest a compound of formula (7), and therefore does not teach or suggest the claimed acetic acid salt of formula (7) as recited in claims 6-8. In addition, Strupczewski does not teach or suggest the claimed acetic acid salt containing more of the Z-isomer than of the E-isomer as recited in claims 4 and 7. Furthermore, Strupczewski does not teach or suggest the claimed acetic acid salt that is at

least 90% isomerically pure of Z-isomer as claimed in claims 5 and 8. For these additional reasons, claims 4-8 would not have been obvious over Strupczewski.

Conclusion

In view of the above arguments, the presently-claimed subject matter is novel and unobvious over the applied prior art. Reconsideration and withdrawal of the rejections and allowance of the present application are respectfully requested.

Should the Examiner have any questions regarding this application, she is encouraged to contact Mark R. Buscher (Reg. No. 35,006) at telephone No. 703 753 5256.

Respectfully submitted,

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